REMARKS

The invention relates to a method for predicting a prognosis in a patient with an acute coronary syndrome. The method involves testing a body fluid from the patient for two markers using an antibody-based assay (*e.g.*, an immunoassay). One marker is cardiac Troponin-T, cardiac Troponin-I, CK-MB, or C-reactive protein; and the second marker is BNP, NT-proBNP or pro-BNP. Binding of the antibodies to the markers in the body fluid sample provides a mechanism to determine a prognosis for the patient.

Claims 23-38 are currently pending in the application. Claims 23-28, 32-34, and 38 are currently under examination, with the remaining claims having been withdrawn from consideration by the Examiner as being drawn to a non-elected invention. No amendments to the claims are made in this submission.

Applicants respectfully request reconsideration of the claimed invention in view of the following remarks.

Non-Art Based Remarks

Rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 112, second paragraph

Applicants respectfully traverse the rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 112, second paragraph, as allegedly failing to comply with the definiteness requirement.

The rejected claims refer to the use of at least two polypeptide markers, one of which is BNP, NT-proBNP, or pro-BNP, and the other of which is cardiac troponin I, or cardiac troponin T (independent claims 23 and 25), or cardiac troponin I, cardiac troponin T, CK-MB, or C-reactive protein (independent claims 27 and 33), in methods for assigning a prognosis (*e.g.*, a likelihood of death) to a patient. These methods comprise performing at least two immunoassays for the polypeptide markers on a sample from the patient, and determining the binding of the markers to their respective antibodies -- that is, determining the results of each of the immunoassays performed.

The assay results thus obtained are used to assign the prognosis of interest to the subject. For example, claims 23, 25, and their dependent claims state "whereby said binding provides a

means for determining cardiac mortality rate." Claims 27, 33, and their dependent claims are perhaps more explicit, in that they provide a step of "relating said binding to said prognosis."

The rejection of these claims is premised on an allegation that "it is not clear how cardiac mortality rate is predicted," and that the claims "[do] not indicate how the prediction is made." Office Action, page 3. The Examiner also raises several questions that are presumed to result from this alleged indefiniteness ("Would the mere presence of a marker, i.e., any binding detection, indicate mortality rate? What would the rate be? Would all markers have to be present? Or would there just be a comparison to a control? What kind of comparison? What increased level of marker(s) must there be?"). *Id.*

As an initial matter, Applicants note that the Board of Patent Appeals and Interferences recently pointed out that the threshold for establishing indefiniteness is very high, and that even a "lack of clarity" is insufficient to establish indefiniteness. Instead, a claim must reach the level of being "insolubly ambiguous" in order to be indefinite:

> The threshold for indefiniteness is very high: the claim must be "insolubly ambiguous". . . . If one of skill in the art would understand the scope of the claim when read in light of the specification, then the claim complies with § 112(2). Claims need not be models of clarity. As long as the meaning is discernible, then even if construction is difficult and the result equivocal, the claim is nevertheless definite. Exxon Research & Eng'g Co., 265 F.3d at 1375, 60 USPQ2d at 1276; All Dental Prodx LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 779-80, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002) (no indefiniteness despite the lack of clarity).

Scripps Research Institute v. Nemerson and Konigsberg, 78 U.S.P.Q.2d 1019, 1030 (Bd.Pat.App & Interf. 2005).

Given the fact that the language complained of by the Examiner in claims 23 and 25 ("whereby said binding provides a means for determining cardiac mortality rate") was present in the now-rejected claims when they were deemed allowable previously, and the fact that the language was also present in the claims throughout an interference which resulted in a formal notice of allowance of the now-rejected claims, Applicants respectfully submit that the claims cannot plausibly be considered "insolubly ambiguous." With respect to the language in claims 27

and 33 ("relating said binding to said prognosis"), Applicants respectfully submit that it is difficult to imagine a clearer English language formulation that describes this step.

Moreover, rather than being indicative of indefiniteness, the Examiner's allegations and the questions posed by the Examiner relate to the breadth of the claims. The fact that the claims embrace different ways in which the immunoassay results may be used to assign a mortality rate to a patient does not equate to a failure to meet the definiteness requirement. *See, e.g.*, MPEP § 2173.04 ("Breadth is not Indefiniteness"). Additionally, the allegations reflect a failure to consider the knowledge available to the skilled artisan and/or the content of the specification. When properly considered, it is apparent that the present claims comply with the definiteness requirement.

In a previous response to the Examiner (see pages 7-8), Applicants discussed in detail some of the many ways that the claims might be practiced, making reference to the art cited by the Examiner. That discussion is not repeated here and the Examiner is referred to the previous text. It is respectfully submitted that the publications cited by the Examiner in support of the rejection rather indicate that the skilled artisan understands that there are multiple different methods by which assay results may be used to assign a prognosis to a patient. As such, the precise methods to be used are best left to the discretion of the skilled artisan, depending for example upon the level of sensitivity and specificity desired from the method. Determining the relationship of one or more marker levels to mortality is a straightforward determination that may be performed for example by assaying the marker(s) in appropriate subject populations (*e.g.*, ACS subjects that die by some endpoint vs. those that do not), and selecting a desired method for assigning a risk of death.

Consistent with the foregoing, the present specification describes on page 5, last full paragraph, that a prognosis is often determined by examining one or more prognostic indicators. On page 6, first full paragraph, the present specification teaches that correlating marker levels to a particular outcome is often performed by comparing a level in a patient to levels in a subject population exhibiting a particular characteristic. In the next three paragraphs, the present specification indicates that this might be performed by merely checking the presence or absence

of a marker level. Alternatively, a threshold level or a nomogram (such as might be represented by a binning strategy) might be used.

Again, the fact that the present claims are sufficiently broad to capture these various methods for relating assay results to a prognosis does not equate to a failure to meet the definiteness requirement. MPEP § 2173.04. Rather, all that is required is that, when the claims are read in the light of the specification and with the knowledge available to the skilled artisan, the artisan is reasonably apprised of the scope of the invention. Because the English language is not always precise, a claim must reach the level of being "insolubly ambiguous" in order to be indefinite. Applicants respectfully submit that the present claims are not "insolubly ambiguous," and so meet the definiteness standard.

Because the claims reasonably apprise the artisan of the scope of the invention, and because 35 U.S.C. § 112, second paragraph demands no more, Applicants urge the Examiner to withdraw the definiteness rejection of claims 23-28, 32-34, and 38.

Art Based Remarks

Rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski, U.S. Patent 5,290,678, in view of Antman *et al., N. Engl. J. Med.* 335: 1342-49, 1996, and further in view of Richards *et al., Heart* 81: 114-120, 1999.

A. The rejection fails for lack of motivation to combine and/or improper use of hindight

A clear flaw in the Examiner's understanding of the claimed invention is readily apparent from the initial analysis offered by the Examiner, which states that "Jackowski teaches the invention substantially as claimed." Office Action, page 4. Quite to the contrary, the present claims require performing assays that detect two markers: a first marker that is a "traditional" cardiac necrosis marker and is selected from the group consisting of cardiac Troponin-T and cardiac Troponin-I (independent claims 23 and 25), or the group consisting of cardiac troponin I, cardiac troponin T, CK-MB, and C-reactive protein (independent claims 27 and 33); and a

second marker that is selected from the group consisting of BNP, NT-proBNP, and pro-BNP. Nowhere in the Jackowski patent is BNP, NT-proBNP, or pro-BNP mentioned, or even contemplated. Indeed, the Examiner acknowledges this fact in the very next paragraph of the Office Action – "Jackowski does not teach detecting the combination of troponin and BNP, nor for the purpose of detecting cardiac mortality" (Office Action, page 5), making the assertion that "Jackowski teaches the invention substantially as claimed" all the more curious.

Given that nothing of record discloses combining a measurement of one of the stated cardiac necrosis markers (*e.g.*, cardiac troponin (I or T) with a measurement of BNP (or its biosynthetically related polypeptides NT-proBNP, and pro-BNP) for prognosis in acute coronary syndromes ("ACS"), the rejection relies on Antman *et al.*, for the alleged teaching that cardiac troponin I measurements are predictive of mortality in patients with ACS, and separately on Richards *et al.*, for the alleged teaching that BNP measurements are predictive of mortality in patients after acute myocardial infarction. The Examiner seeks to combine these two publications in order to arrive at the presently claimed invention

The alleged motivation offered for combining the teachings of Antman *et al.* and Richards *et al.* is that "Richards et al. teach that BNP is a powerful predictor of death in patients with acute myocardial infarction . . . and that adding BNP as a marker to a multivariate analyses added additional information in predicting death (see page 118, right col., last paragraph)." Office Action, page 6. To the extent that the Examiner's reasoning, which is based on a partial quote of a sentence from Richards *et al.*, implies that the cited art indicates BNP measurements "added additional information" to cardiac troponin measurements, the reasoning is incorrect. In fact, the cited section of Richards *et al.* states that BNP measurements "added additional information beyond clinical features, noradrenaline concentrations, and LVEF [left ventricular ejection fraction] in predicting heart failure or the composite end point of death and/or heart failure." Nothing in Richards *et al.* mentions or even contemplates combining BNP measurements with cardiac troponin measurements as the Examiner asserts, much less indicates that the two measurements might add "additional information" to one another.

Ignoring these inaccuracies underlying the obviousness rejection, and the fact that the

subject matter of the present claims has been deemed allowable over the art at least twice previously by the Office, Applicants provide the following comments on the merits of the rejection.

To the best of Applicants understanding, the rejection may be best viewed as an assertion that combining BNP measurements with cardiac troponin measurements would be *prima facie* obvious, as the prior art allegedly teaches that each marker individually is useful for the same purpose -- specifically, prediction of death in patients with acute myocardial infarction.

Applicants respectfully submit that the Examiner has simply identified two publications, Antman *et al.* regarding cardiac troponin I measurements, and separately Richards *et al.* regarding BNP measurements, and asserted it would be obvious to combine them to provide the claimed invention. In fact, no publication of record discloses or suggests to combine BNP and cardiac troponin measurements for assigning prognosis in ACS patients. U.S. Patent No. 6,461,828, which was the subject of an interference with the present patent application (resolved in favor of the present application's priority) includes a list in Table 1 of literally thousands of possible markers supposedly related to cardiac injury.[1] From the potential pool of possible markers, the Examiner would select two – BNP and cardiac troponin – for combination. When viewed in this light, it is apparent that the Examiner's selection of BNP and cardiac troponin measurements, from amongst thousands of possible choices, to arrive at a method for assigning prognosis in ACS patients can only be made improperly based on hindsight using Applicants' disclosure or the use of an "obvious to try" rationale. Neither hindsight nor an "obvious to try" rationale is sufficient to establish a *prima facie* case of obviousness. *See, e.g., In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988) ("The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure").

B. Secondary Considerations require that the claimed invention be found non-obvious

[1] The generic terms "protein kinase" and "protein phosphatase" alone represent thousands of different proteins.

Even assuming solely for the sake of argument that a prima facie case has been stated, such would be rebutted by a showing of unexpected results and acclimation (tributes paid to and adoption of the invention by others). In this regard, Applicants provide the following comments.

It was unexpected and surprising that BNP measurements and cardiac necrosis markers such as troponin measurements would provide independent prognostic information in acute coronary syndromes ("ACS"), and so when combined, would provide improved ability to stratify risk in patients in comparison to either BNP or cardiac troponin alone. In fact, the prior art would lead the skilled artisan to erroneously believe that BNP (and the related peptides such as NT-pro BNP), to the extent it would provide any information at all, would provide similar information to cardiac necrosis markers such as troponin, and not independent information. Additionally, it was unexpected that BNP measurements and cardiac troponin measurements would provide independent prognostic information across the entire spectrum of ACS conditions, and not only in acute myocardial infarction. The importance of Applicants' contribution in this regard has been widely recognized, acknowledged, and adpoted in the art. These superior and unexpected properties of the claimed invention, and the secondary considerations represented by the widespread approval and adoption of the claimed invention in the art, rebut any *prima facie* case of obviousness that may have been established by the Examiner. *See, e.g.*, MPEP § 716.02(a).

The filing date of the present application is April 13, 2001. Shortly thereafter, the data and conclusions contained in the present application were published in the *New England Journal of Medicine,* perhaps the preeminent medical journal in the world. *Compare, e.g.*, Figures 1-4 of de Lemos *et al.*, *N. Engl. J. Med.* 345: 1014-21 (2001) to Figures 1-4 of the present specification. As taught in the present specification and confirmed through subsequent publication in the *NEJM*, the present inventors discovered that BNP measurements and cardiac troponin measurements provide independent prognostic information in ACS patients (*see, e.g.*, specification, page 13, first full paragraph). This discovery was considered so important and so unexpected that it was not only deemed worthy of publication in the *NEJM*, but the *NEJM*'s editors also published an Editorial in the same *NEJM* issue, emphasizing the importance of the discovery to its readers:

Use of the clinical characteristics of the patient, the electrocardiographic findings, and the levels of traditional serum markers of myocyte necrosis, such as the creatine kinase MB fraction and troponin I, is only partially successful in risk stratification. In patients who have unstable angina or myocardial infarction without ST-segment elevation, an elevated troponin level confers an increased short-term risk of death. However, as compared with data from cohort studies, data from clinical trials reveal that the troponin level has less prognostic value. One recent study demonstrated that the measurement of three markers of myocyte necrosis — troponin I, creatine kinase MB, and myoglobin — significantly increased physicians' ability to detect acute coronary syndromes, as compared with the use of each marker alone. However, a patient who has unstable angina but no evidence of myocyte necrosis still has underlying rupture or erosion of plaques and may still have an increased risk of cardiac events.

As our understanding of the pathophysiology of the acute coronary syndromes advances, our ability to stratify patients according to risk improves in tandem. This issue of the *Journal* contains two articles — one by de Lemos et al. and one by Bayes-Genis et al. — on important new markers for use in risk stratification for acute coronary syndromes based on neurohormonal activation and inflammation. De Lemos and colleagues measured plasma levels of brain (B-type) natriuretic peptide, a natriuretic and vasodilative peptide regulated by ventricular wall tension and stored mainly in the ventricular myocardium, in 2525 patients with acute coronary syndromes. A single measurement of B-type natriuretic peptide obtained a median of 40 hours after the onset of ischemic symptoms predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, or unstable angina, as well as the risk of new or progressive congestive heart failure and new or recurrent myocardial infarction. Moreover, the relation between the long-term risk of death and the B-type natriuretic peptide level was independent of electrocardiographic changes, troponin I levels, renal function, and the presence or absence of clinical evidence of congestive heart failure. Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

Rabbani, *N. Engl. J. Med.* 345: 1057-59 (2001) (emphasis added) (reference A9 to SB08, concurrently filed herewith).

Within less than one year of the publication of this data from the present application in *NEJM*, researchers published a similar article concerning the biosynthetically related polypeptide NT-proBNP, demonstrating that NT-proBNP and cardiac troponin measurements also provide independent prognostic information in ACS, and stating that BNP and NT-proBNP are

"remarkably similar" in this regard. *See*, Omland *et al., Circulation* 106: 2913-18 (2002) (reference A8 to SB08, concurrently filed herewith).

One reason for the surprising nature and importance of this finding may be gleaned from the prior art, as discussed in detail by Dr. Norman Alan Paradis in a declaration accompanying this response. As Dr. Paradis states in paragraph 5 of his declaration, prior to the present discovery Hassan and co-workers reported in *Médecine Nucléaire* 24: 301-10 (2000) (reference A47 to SB08, concurrently filed herewith) on the use of thallium-201 single photon emission computerized tomography (Tl-201 SPECT) to distinguish subjects having necrotic myocardium from subjects having ischemic myocardium. Hassan *et al.* also examined plasma BNP concentrations in these two groups, and concluded that BNP was significantly increased in the case of cardiac necrosis. On the other hand, BNP did not increase due to cardiac ischemia. This fact would lead the skilled artisan to conclude that BNP, like cardiac troponin, is nothing more than a marker of cardiac necrosis, and that BNP and cardiac troponin would not be independent markers. As demonstrated in the present specification, such a conclusion is incorrect.

The practical importance of discovering that BNP and cardiac troponin measurements provide independent prognostic information in ACS is also discussed in detail in paragraph 10 of the Paradis declaration. Sabatine *et al.*, *Circulation* 105: 1760-63, 2002, reports on the use of BNP, cardiac troponin I, and an inflammatory marker (C-reactive protein, or CRP) in a "multimarker strategy" for risk stratification in non-ST elevation ACS. As noted by the authors of that study, each of these markers can "provide unique prognostic information in patients with ACS. A simple multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation allows risk stratification over a broad range of short- and long-term major cardiac events." Sabatine *et al.*, Abstract. These results are of a significant practical advantage, as the combined markers provide an improved prognosis of ACS patients.

According to Dr. Paradis, this practical advantage has been widely recognized, acknowledged, and adopted in the art, as demonstrated by the following excerpt from Silver *et al.*, "BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular

Disease," *CHF* 10[5 Suppl. 3] 1-30 (2004) (reference A12 to SB08, concurrently filed herewith). In this report, prepared by "an expert panel... gathered by selecting clinicians and scientists with expertise with the natriuretic peptide system," the practical advantage of combined measurements of BNP and cardiac troponin is made clear:

> 7.2 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Multimarker panels that include BNP troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes.

In addition, the present invention is applicable not just in acute myocardial infarction, but also "provides powerful risk-stratification across the entire spectrum of acute coronary syndromes," including for example unstable angina. Specification, page 12, last full paragraph. By way of contrast, the Richards *et al.* article cited by the Examiner in the rejection evaluated a subject population that featured only individuals having ST-elevation myocardial infarction. *See, e.g.*, Richards *et al., Heart* 81: 114-120 (1999), page 114, right column, first paragraph of "Methods" ("Acute myocardial infarction was defined by... ischaemic change on the ECG in two or more continuous leads..."). Thus, the publications of record, including the cited Richards *et al.* article, are silent on the use of BNP measurements in ACS conditions other than acute myocardial infarction.

While the cited art focuses only on this ST-elevation myocardial infarction population, the present invention reports for the first time that BNP is an independent prognostic marker, relative to cardiac troponins, across the entire spectrum of ACS conditions including conditions such as myocardial infarction without ST-segment elevation and unstable angina. As discussed by Dr. Paradis in paragraphs 7 and 8 of his declaration, this feature of the present invention was again of such significance that its publication in the de Lemos *et al. NEJM* article warranted special mention in the accompanying Rabbani editorial (*N. Engl. J. Med.* 345: 1057-59 (2001)):

> A single measurement of B-type natriuretic peptide obtained a median of 40 hours after the onset of ischemic symptoms predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction

> without ST-segment elevation, or unstable angina, as well as the risk of new or progressive congestive heart failure and new or recurrent myocardial infarction.... Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

That the claimed invention can provide prognostic information across the entire spectrum of acute coronary syndromes was unexpected because the scientific literature at the time indicated that BNP measurements would not be applicable outside of the context of acute myocardial infarction. Acute myocardial infarction refers to necrosis of the myocardium. *See, e.g.*, Definition of myocardial infarction, published jointly by the American College of Cardiology and the Joint European Society of Cardiology, *J. Am. Coll. Cardiol.* 36: 959-969, (2000), heading II. Other ACS conditions, such as unstable angina, are by definition diseases of ischemia, but not diseases of necrosis. According to Dr. Paradis, this teaching in Hassan *et al.* indicates to the artisan that, contrary to the findings of the present inventors, BNP should not be expected to provide any information on conditions that do not involve necrosis of the myocardium. Given such a teaching that BNP would not be increased outside of the context of acute myocardial infarction, Dr. Paradis concludes that one of ordinary skill was surprised to learn that BNP is an independent prognostic marker, relative to cardiac troponins, even in ACS conditions such as unstable angina. Paradis declaration, paragraph 9.

Again, these results are of a significant practical advantage, as the combined markers provide a more effective tool for identifying patients at increased risk for clinically important cardiac events.

C. The present claims are non-obvious over the cited combination of art

In conclusion, nothing of record discloses combining the measurement of cardiac necrosis markers (such as cardiac troponin I or T) with the measurement of BNP (or its biosynthetically related polypeptides NT-proBNP, and pro-BNP) for prognosis in ACS," and the proposed combination of Antman *et al.* with Richards *et al.* can only be made by the improper use of hindsight with the benefit Applicants' disclosure. Moreover, the superior and unexpected properties of the claimed invention, and the secondary considerations represented by the

widespread approval and adoption of the claimed invention in the art, rebut any *prima facie* case of obviousness that may have been established by the Examiner.

In view of the foregoing, Applicants urge the Examiner to withdraw the obviousness rejection of claims 23-28, 32-34, and 38.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 10/25/2006

By _____

FOLEY & LARDNER, LLP
P.O. Box 80278
San Diego, CA 92138-0278
Telephone: (858) 847-6721
Facsimile: (858) 792-6773

Richard J. Warburg, Registration No. 32,327
Attorney for Applicant
By Barry S. Wilson, Registration No. 39,431